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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/915,060	07/25/2001	Sigrid Cornelis	4976US	6077

24247 7590 08/28/2002

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EXAMINER	
SULLIVAN, DANIEL M	

ART UNIT	PAPER NUMBER
1636	15

DATE MAILED: 08/28/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

File

Office Action Summary	Application No.	Applicant(s)	
	09/915,060	CORNELIS ET AL.	
	Examiner	Art Unit	
	Sita Pappu	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 June 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-7,11-17 and 23-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-7,11-17 and 23-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 June 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1, 4-7, 11-17, 21, 23-36 are pending in the instant application. This Office Action is in response to the amendment filed by the Applicant in paper # 10 on 06/19/2002. Claims 1, 4-7, 11-17, 21, 23-36 are under consideration.

Response to the amendment

Claims 2, 3, 8-10, 18, 19, 22 are cancelled. Claims 1, 4, 11, 12, 14, 17 are amended. New claims 25-36 are added. Currently, claims 1, 4-7, 11-17, 21, 23-36 are under consideration.

Formal Drawings submitted 06/19/2002 (Paper # 13), are approved by the draftsperson.

All rejections of claims 2, 3, 8-10, 18, 19, 22 have been rendered moot in light of cancellation of these claims (paper # 10, filed 06/19/2002).

The rejection of claim 16 under 35 U.S.C. 103(a) has been withdrawn in light of Applicant's amendment and arguments.

Claims 1, 4-7, 11, 12 stand rejected under 35 U.S.C. 102(b) for reasons of record and as discussed, herein, below.

Claims 13-15, 17, 23, 24 stand rejected under 35 U.S.C. 103 (a) for reasons of record and as discussed, herein, below.

Claims 25, 27-36 are newly rejected under 102(a) as being anticipated by Gururajan et al. (1998, Genome research, Vol. 8, No. 9, 929-939).

Claims 16, 17, 26 are newly rejected under 35 U.S.C. 112, first paragraph for lack of enablement.

Response to Arguments

In response to the rejection of claims 1, 4-7, 11, 12 under 102(b), and claims 13-15, 17, 23, 24 under 103(a), Applicant argues (page 6, paragraph 5) that Xiang is devoid of any teaching or suggestion of initiating mRNA translation at an IRES site in a eukaryotic cell.

These arguments have been considered but are not found persuasive for the following reasons.

Since the claim is directed to a composition, the intended use of the claimed composition is given patentable weight when making a determination of patentability under 35 U.S.C. 102 only when it serves to define a structural requirement. In composition claims, intended use must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. Furthermore, the preamble is generally nonlimiting if it merely recites an inherent property. See MPEP 2111.02. In the instant case, the prior art structure has all the features required to perform the intended use recited in the claims. The function of initiating mRNA translation at an IRES site in a eukaryotic cell is an inherent property of the sequence taught by Xiang et al. The claiming of a new use, new function, or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. *In re Best* 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977). See also MPEP 2112.

Claim 1 is directed to an isolated and/or recombinant nucleotide sequence enabling a G2/M cell cycle dependent initiation of translation of mRNA, wherein the nucleotide sequence is an IRES sequence that initiates mRNA translation in a eukaryotic cell.

Xiang et al. (1994) teach expression of the β1 isoform of PITSLRE protein kinases, that is substantially homologous to the α2-2 isoform, in a reticulocyte lysate cell system through the use of a vector (see page 15787, paragraph 2 in Experimental Procedures, lines 1-5 and lines 31-34). Further, Xiang et al. (1994) teach the nucleotide sequence of the α2-2 isoform of the instant case. However, they do not teach the expression in a eukaryotic cell with the α2-2 isoform of PITSLRE kinases.

Considering the substantial homology between the two isoforms as indicated by Xiang et al. (1994) in Figure 3 on page 15790, there is a reasonable expectation that similar results would have been achieved if the α2-2 isoform was used in place of the β1 isoform in the studies done by Xiang et al. (1994). It is well known in the art that isoforms and isolates of genes and organisms behave similarly when there is high sequence homology between the said genes and/or organisms.

Further, as stated, herein above, the claiming of a new use, new function, or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. The property of enabling a G2/M cell cycle dependent initiation of translation of mRNA, wherein the nucleotide sequence is an IRES sequence that initiates mRNA translation in a eukaryotic cell is a property that is inherently present in the sequence taught by Xiang et al.

Thus, the claimed compositions and methods are anticipated and/or made obvious by the prior art.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 16, 17, and 26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for in vitro methods of initiating translation in a eukarytotic cell, does not reasonably provide enablement for the practice of said methods in vivo and for therapeutic purposes. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

Nature of the Invention and the Breadth of the Claims:

Claims 16, 17 and 26 are directed to methods of initiating translation of mRNA in a cell by introducing an expression vector comprising a translation control element into the cell. The specification contemplates the use of the claimed methods in gene therapy (page 4, paragraph 0011, page 10, paragraphs 0037, 0038). Thus, the intended use of the methods encompasses gene therapy and, thus, the nature of the invention is directed toward gene therapy using the isolated nucleic acid molecule of the instant invention in a vector, and thus, the claims have a very broad scope.

State of the art:

At the time of filing, *in vivo* gene therapy utilizing the direct administration of recombinant nucleic acids, whether in the form of retroviruses, adenoviruses, or plasmid DNA/liposome complexes, was considered to be highly unpredictable. Verma et al. states that, "[t]he Achilles heel of gene therapy is gene delivery..", and that, "most of the approaches suffer from poor efficiency of delivery and transient expression of the gene" (Verma et al. (1997) Science, Vol. 389, page 239, column 3, paragraph 2). Marshall concurs, stating that, " difficulties in getting genes transferred efficiently to target cells- and getting them expressed- remain a nagging problem for the entire field", and that, "many problems must be solved before gene therapy will be useful for more than the rare application" (Marshall (1995) Science, Vol. 269, page 1054, column 3, paragraph 2, and page 1055, column 1).

Orkin et al. further states in a report to the NIH that, " .. none of the available vector systems is entirely satisfactory, and many of the perceived advantages of vector

systems have not been experimentally validated", and that," [w]hile the expectations and the promise of gene therapy are great, clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol" (Orkin et al. (1995) "Report and recommendations of the panel to assess the NIH investment in research on gene therapy", page 1, paragraph 3, and page 8, paragraph 2).

Among the many factors that the art teaches affect efficient gene delivery and sustained gene expression are anti-viral immune responses, particularly against adenoviral proteins, and the identity of the promoter used to drive gene expression. Verma et al. teaches that weak promoters produce only low levels of protein, and that only by using appropriate enhancer-promoter combinations can sustained levels of therapeutically effective protein expression be achieved (Verma et al., *supra*, page 240, column 2). Verma et al. further warns that, " .. the search for such combinations is a case of trial and error for a given type of cell" (Verma et al., *supra*, page 240, bridging sentence of columns 2-3). The state of the art is such that no correlation exists between successful expression of a gene and a therapeutic result (Ross et al. Human gene Therapy, vol. 7, pages 1781-1790, September 1996, see page 1789, column 1, first paragraph). Thus, the art at the time of filing clearly establishes that expectation for achieving a desired therapeutic effect *in vivo* by expressing a therapeutic gene using any of the expression constructs known in the art at the time of filing was extremely low.

Amount of Direction provided and existence of working examples:

The prior art teaches the unpredictability of gene therapy using nucleic acid sequences and vectors. In cases where prior art does not teach how to use the method,

all the guidance for practicing the invention must come from the specification. The specification fails to disclose any therapeutic uses of the nucleic acid molecule of the instant invention or its use in any gene therapy applications. The only guidance provided in the specification with respect to the therapeutic use is a reference to the applicability of the said molecule for therapeutic purposes (page 4, paragraph 0011, page 10, paragraphs 0037, 0038).

Examples in the specification describe the internal initiation of translation on the PITSLRE p110 mRNA by an IRES element present in the coding region (example 1, page 16) and the characterization of the IRES element (example 2, page 19). The specification does not teach therapeutic uses for the IRES element of the instant case for in vivo use. Nor does it teach whether the levels of expression obtained in the cell lines used are sufficient to have a therapeutic effect in treating the various disorders referred to in the specification. Further, the specification fails to teach the modes and frequency of administration of this element needed to have a therapeutic effect, such that one of skill in the art would accept that their method would result in a therapeutic outcome and be able to practice the method using the guidance provided in the specification.

The specification does not provide guidance to overcome the art recognized unpredictabilities of gene therapy because it lacks correlative evidence between the delivery and expression of a gene along with the IRES element in the claimed methods and any therapeutic effect. While the specification demonstrates the transfection of a number of cell lines in vitro using the method of the instant invention, it is not predictable

that the results obtained in vitro correlate to results expected in vivo such that one of skill would have reasonable expectation of obtaining therapeutic levels of expression of any gene of interest.

Predictability of the Art, Amount of Experimentation and Skill level of the artisan:

While it is relatively routine in the gene transfer art to achieve expression at non therapeutic levels, i.e., expression at low levels or at levels providing no patentably useful phenotypic effect, it is unpredictable without specific guidance and direction whether one will achieve expression of a particular molecule at levels sufficient for a therapeutic effect. Thus, when there is deficiency in the art in terms of predictability of obtaining therapeutic levels of expression, the Applicant must provide sufficient guidance and direction which demonstrates or reasonably correlates to therapeutic levels of expression of a DNA product in an art recognized animal model or patient as claimed.

Although the skill of an artisan in this subject area is considered to be very high, it would require undue experimentation on the part of an artisan to make and use the invention as specified in vivo and use the invention as claimed. The specification and the working examples do not provide sufficient guidance to practice the invention in vivo. Therefore, in the absence of specific guidance and working examples, the use of the claimed methods in gene therapy or for any therapeutic use is unpredictable. In such a situation, one skilled in the art would not know how to use the invention in vivo, without undue experimentation. In view of the limited guidance in the specification, and limited working examples, and the unpredictability of the art, one skilled in the art would

be required to engage in undue experimentation, in order to use the claimed invention in vivo.

Thus the specification does not enable one skilled in the art to use the claimed methods in gene therapy.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 25, 27-36 are rejected under 35 U.S.C. 102(a) as being anticipated by Gururajan et al. (1998, Genome research, Vol. 8, No. 9, 929-939).

Gururajan et al. (1998) teach the nucleotide sequence of a human PITSLRE protein kinase gene, Cdc2L1 (see page 929, for GenBank accession numbers) that exhibits 100% sequence identity to SEQ ID NO:4 of the instant invention. Further, Gururajan et al. teach expression of their Cdc2L1 gene in human cell lines and tissues (page 933, right column, subsection 'Expression of Cdc2L1 and Cdc2L2 in human cell lines and tissues').

Thus, Gururajan et al. anticipated the invention of claims 25, 27-36.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sita S Pappu whose telephone number is (703) 305-5039. The examiner can normally be reached on Mon-Fri (8:30 AM - 5:00 PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel can be reached on (703) 305 1998. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308 4242 for regular communications and (703) 872 9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the patent analyst, Tracey Johnson, whose telephone number is (703) 305-2982.

Anne-Marie Baker
ANNE-MARIE BAKER
PATENT EXAMINER

S. Pappu
August 21, 2002